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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Joseph Itskovitz-Eldor

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09/09/2010

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EXAMINER

KIM, TAEYOON

ART UNIT

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1651

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/536,734	Applicant(s) ITSKOVITZ-ELDOR ET AL.	
	Examiner Taeyoon Kim	Art Unit 1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 July 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 193, 194, 197, 199-201, 205 and 214-234 is/are pending in the application.
- 4a) Of the above claim(s) 194, 201 and 216-234 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 193, 197, 199, 200, 205, 214 and 215 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>5/13/10, 6/28/10</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's amendment and response filed on 7/6/2010 has been received and entered into the case.

Claims 1-192, 195, 196, 198, 202-204, 206-213 are canceled, claims 194, 201 and 216-234 have been withdrawn from consideration as being drawn to non-elected subject matter.

Claims 193, 197, 199, 200, 205, 214 and 215 have been considered on the merits. All arguments have been fully considered.

Response to Arguments

Applicant's arguments filed 7/6/2010 have been fully considered but they are not persuasive.

Applicant alleged that the step (d), dissociating the surface bound cell clusters into single cells and culturing the single cells under non-adherent conditions to form suspended cell clusters being enriched with cells capable of secreting insulin, leads to an unexpected formation of the suspended cell cluster, and an unexpected increase in the proportion of insulin secreting cells.

This argument has been fully considered but found not persuasive in the absence of any evidence showing alleged "unexpected and surprising" results obtainable from the step (d).

Applicant alleged that there is no motivation to combine the teaching of Zhao et al. with the teaching of Lumelsky because the teaching of Zhao et al. is directed to adult human beta cells rather than the islets from stem cells. However, the step (c) of the current invention is considered to form insulin-secreting pancreatic cells, that is beta cell, upon the adherent culture, and the resulting cells of the step (c) is considered the similar, if not identical, to the adult islet beta cells.

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Considering that the cells derived from the step (c) are insulin-secreting beta cells since the claim discloses the resulting cells are insulin secreting cells by the limitation of “thereby generating cells capable of secreting insulin”, a person of ordinary skill in the art would certainly try to utilize the method of Zhao et al. to preserve the capacity of the insulin-secreting cells obtained from step (c).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Based on the above discussion, it is considered that the references of record render the claimed invention obvious.

Applicant is advised to provide clear evidence showing the alleged "unexpected and surprising" results obtainable from the step (d) of the current invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 193, 197, 199, 200, and 205 stand rejected under 35 U.S.C. 103(a) as being

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unpatentable over Lumelsky et al. (of record) in view of Dang et al. (of record) in further view of Zhao et al. (2002, Transplantation; of record).

Lumelsky et al. teach a method of producing pancreatic endocrine cells by generating embryoid bodies from ES cells in suspension culture (e.g. culturing cells on non-adherent bacterial culture dishes) (see paragraphs [0093]-[0096]), selecting nestin-positive pancreatic endocrine stem cells (a pancreatic islet cell progenitor) by culturing the cells of embryoid bodies (EBs) on substrate-coated surface (thus forming surface bound cell clusters) (see paragraphs [0096]-[0099]). The pancreatic endocrine stem cells are expanded and differentiated into mature endocrine cells which produce and secrete insulin (see paragraphs [0101]-[0114]).

Although Lumelsky et al. teach isolation of pancreatic precursor cells from EB, it does not particularly teach a step of dissociating EB into single cells displaying at least one characteristic associated with a pancreatic islet phenotype.

Dang et al. teach dissociation of EB into single cells for the subsequent analysis by flow cytometry (p. 444, right col. 2nd para.).

It would therefore have been obvious for the person of ordinary skill in the art at the time the invention was made to dissociate EB of Lumelsky et al. to obtain single cells and isolate cells having pancreatic progenitor phenotype (nestin-positive) by flow cytometry as taught by Dang et al.

Since Lumelsky et al. teach isolation of pancreatic progenitor cells from EB based on the expression of nestin or other specific marker expression (PDX-1, insulin, etc. par. 100), and it is well known in the art that nestin positive cells from EB can be identified by flow cytometry, which requires dissociation into single cells, a person of ordinary skill in the art would have been

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motivated to try the dissociation technique of Dang et al. to obtain dissociated EB for identification of nestin-positive pancreatic progenitor cells.

Although Lumelsky et al. do not particularly teach a culturing condition suitable for formation of surface bound cell clusters and inhibiting growth of non insulin producing cells (step (c) of claim 193), since Lumelsky et al. utilize serum free media such as ITSF for the culture of pancreatic precursor cells and these cells are plated onto a surface that permits adhesion of pancreatic endocrine stem or progenitor cells (para. 98 and 99), the method of Lumelsky et al. inherently promote formation of surface bound cell clusters and inhibiting growth of non-insulin producing cells as claimed in the current invention.

Lumelsky et al. do not teach a step (d) of dissociating the surface bound cell clusters into single cells and forming suspension culture to obtain suspended clusters of insulin secreting cells.

Zhao et al. teach suspension culture of islets (cluster-cultured cells) preserves the capacity of adult human islets to express insulin during the long-term culture, and this capacity is enhanced significantly by transplantation into a recipient (see Abstract).

It would therefore have been obvious for the person of ordinary skill in the art at the time the invention was made to combine the method steps of Zhao et al. in the method of Lumelsky et al. in view of Dang et al.

The skilled artisan would have been motivated to make such a modification because Zhao et al. teach the suspension cluster culture of islet cells provides preservation of insulin expression of the cells and significant enhancement of insulin expression upon transplantation, and a person of ordinary skill in the art would recognize this as a benefit for transplantation of islets for

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patients in need of such treatment.

Although Lumelsky et al. do not particularly disclose that the proportion of pancreatic endocrine cells being at least 4 percent (claim 199), since it is disclosed that more than about 50%, 80% or 90% of the cell culture being pancreatic stem cells (see paragraph [0100]), it would have been obvious to consider that pancreatic endocrine cells differentiated from the pancreatic stem cells being more than 4%.

With regard to the insulin secretion rate of at least 6 microunits of insulin per one hundred thousand cells per hour (claim 200), this limitation is considered as a property of cells resulted from the method of the current application. The “wherein” clause in the claim merely states the result of the limitations in the claim, and therefore, it adds nothing to the patentability or substance of the claim. Therefore, this phrase does not limit the claim. See *Texas Instruments Inc. v. International Trade Commission*, 26 USPQ2d 1010 (Fed. Cir. 1993); *Griffin v. Bertina*, 62 USPQ2d 1431 (Fed. Cir. 2002); *Amazon.com Inc. v. Barnesandnoble.com Inc.*, 57 USPQ2d 1747 (Fed. Cir. 2001). Nevertheless, the insulin producing cells of Lumelsky et al. are considered to have the same intended results as the claimed invention in the absence of evidence to the contrary.

With regard to the limitation directed to the trypsinization step of surface bound cell clusters (claim 205), it is not only well known in the art that adherent cells can be dissociated with trypsinization but also Zhao et al. teach a trypsinization step of surface bound cells (p.1455, left col. under “Materials and Methods”).

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

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Claims 193, 214 and 215 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lumelsky et al. (supra) in view of Dang et al. (supra) in further view of Zhao et al. (supra) and Thomson et al. (of record).

Lumelsky et al. in view of Dang et al. in further view of Zhao et al. render the limitations of claim 193 and 214 obvious (see above).

Lumelsky et al. in view of Dang et al. in further view of Zhao et al. do not teach the use of H13 cells.

Thomson et al. teach that H13 cell line is an embryonic stem cell line derived from human blastocysts (see whole document; p.1145, middle column; Fig. 2).

It would therefore have been obvious for the person of ordinary skill in the art at the time the invention was made to replace the human ES cells of Lumelsky et al. with H13 cells of Thomson et al. in the method of Lumelsky et al. because a person of ordinary skill in the art would recognize the H13 cells of Thomson et al. would be art-acceptable equivalent to the human ES cells of Lumelsky et al.

M.P.E.P. §2144.06 states “In re Scott, 323 F.2d 1016, 139 USPQ 297 (CCPA 1963) (Claims were drawn to a hollow fiberglass shaft for archery and a process for the production thereof where the shaft differed from the prior art in the use of a paper tube as the core of the shaft as compared with the light wood or hardened foamed resin core of the prior art. The Board found the claimed invention would have been obvious, reasoning that the prior art foam core is the functional and mechanical equivalent of the claimed paper core. The court reversed, holding that components which are functionally or mechanically equivalent are not necessarily obvious in view of one another, and in this case, the use of a light wood or hardened foam resin core does

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not fairly suggest the use of a paper core.); *Smith v. Hayashi*, 209 USPQ 754 (Bd. of Pat. Inter. 1980) (The mere fact that phthalocyanine and selenium function as equivalent photoconductors in the claimed environment was not sufficient to establish that one would have been obvious over the other. However, there was evidence that both phthalocyanine and selenium were known photoconductors in the art of electrophotography. “This, in our view, presents strong evidence of obviousness in substituting one for the other in an electrophotographic environment as a photoconductor.” 209 USPQ at 759.).”

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taeyoon Kim whose telephone number is (571)272-9041. The examiner can normally be reached on 8:00 am - 5:00 pm ET (Mon-Thu).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Taeyoon Kim/
Primary Examiner, Art Unit 1651